REMARKS/ARGUMENTS

With this amendment, claims 1-12 and 20-21 are pending. Claims 13-19 are cancelled without prejudice to subsequent revival. New claims 20 and 21 are added. For convenience, the Examiner's rejections are addressed in the order presented in an February 7, 2007, Office Action.

I. Status of the claims

Claims 64 and 112 are amended to recite treatment of interferon sensitive cancers. Support for this amendment is found throughout the specification, for example at paragraph 58 and original claim 65. Claim 64 is amended to recite a synthetic interferon enhancer. Support for this amendment is found throughout the specification, for example at paragraph 57. Claim 64 is also amended to recite that the IMPDH inhibitor enhances interferon induction. Support for this amendment is found throughout the specification, for example at paragraphs 153, 156, and 157. Claim 65 is amended to recite specific interferon sensitive cancers. Support for this amendment is found throughout the specification, for example at paragraph 57. These amendments add no new matter.

II. Claim objections

Claims 69-82 are objected to because they depend from cancelled claim 14. In order to expedite prosecution, the limitations of claim 14 are added to claim 69. In view of this amendment, withdrawal of the objection to claims 69-82 is respectfully requested.

III. Rejections under 35 U.S.C. §112, second paragraph

Claims 69-82 are rejected under 35 U.S.C. §112, second paragraph, as allegedly omitting essential steps. In order to expedite prosecution, the formula for the nucleic acid of claim 14 is added to claim 69. In view of this amendment, withdrawal of the rejection under 35 U.S.C. §112, second paragraph is respectfully requested.

IV. Rejections under 35 U.S.C. §112, first paragraph, enablement

Claims 64-82 and 112-113 are rejected under 35 U.S.C. §112 first paragraph, because the specification allegedly does not enable the full scope of the claims. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection. The rejection raises two issues. Claims 64-66, 68-82, and 112-113 are rejected because the specification allegedly does not provide enablement for any IMPDH inhibitor or for prodrugs of those compounds. The Office Action does indicate that claims that recite specific IMPDH inhibitors are enabled. claims 64, 65, 67-82, and 112 are rejected because the specification allegedly does not provide enablement for treatment of any cancer. The Office Action does indicate that treatment of a leukemia, a lymphoma, a myeloma, a melanoma, or a renal cancer is enabled.

The Examiner appears to have focused improperly on inoperative embodiments, leading to the conclusion that undue experimentation would be required to use the claimed methods. However, the proper test of enablement is "whether one skilled in the art could make or use the claimed invention from the disclosure in the patent coupled with information known in the art without undue experimentation" (*see, e.g.*, MPEP §2164.01). In the present application, one of skill would know how to avoid inoperative embodiments without undue experimentation (*see, In re Cook and Merigold*, 169 USPQ 299, 301 (C.C.P.A. 1971)). Moreover, the present application provides guidance in the form of assays and working examples for enhancement of interferon induction by administration of an IMPDH inhibitor and an interferon inducer.

Claims reading on inoperative embodiments are enabled if the skilled artisan understands how to avoid inoperative embodiments. As described by the court in *In re Cook and Merigold*, 169 USPQ 302:

> Many patented claims read on vast numbers of inoperative embodiments in the trivial sense that they can and do omit 'factors which must be presumed to be within the level of ordinary skill in the art'....There is nothing wrong with this so long as it would be obvious to one of ordinary skill in the relevant art how to include those factors in such a manner as to make the embodiment operative rather than inoperative.

See, In re Cook and Merigold, 169 USPQ at 302 (quoting in part *In re Skrivan*, 166 USPQ 85, 88 (C.C.P.A. 1970)).

Factors such as the amount of guidance presented in the specification and the presence of working examples must be considered to determine whether undue experimentation is required to practice the claimed invention (*see*, *Ex Parte Forman*, 230 USPQ 546 (Bd. Pat. App. & Int. 1985) and *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988)). As described in *Wands*, "a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed" (*see*, *Wands*, USPQ2d at 1404, quoting *In re Jackson*, 217 USPQ 804 (Bd. Pat. App. & Int. 1982)).

With regard to the rejection based on use of IMPDH inhibitors or prodrugs, Applicants respectfully assert that the claims are directed to methods of use of such compounds and not to novel IMPDH inhibitors. Those of skill are well-aware of assays for IMPDH inhibition activity. *See, e.g.* Albrecht *et al.* DE 19811313, cited in the Office action at page 18. The specification also teaches those of skill that the enhancement of interferon induction caused by an IMPDH inhibitor is abolished by addition of guanosine to a cell culture. *See, e.g.*, specification at paragraph 292.

With regard to prodrugs, many known IMPDH inhibitors are prodrugs or have prodrugs, demonstrating that those of skill are able to identify such compounds without undue experimentation. Thus, the disclosure of the specification is adequate to allow those of skill to use the claimed methods. *See, e.g.*, speciation at paragraph 52, replicated below for the Examiner's convenience.

> **[0001]** An "IMPDH inhibitor" refers to an inhibitor of the enzyme inosine monophosphate dehydrogenase. Currently, three IMPDH inhibitors are used clinically: ribavirin, mizoribine, and mycophenolate mofetil. Ribavirin and mizoribine are prodrugs that are phosphorylated intracellularly to produce IMP analogs (Goldstein et al., *Cuff Med Chem*, 6:519-536 (1999)). Viramidine is a prodrug of Ribavirin. Mycophenolate mofetil is immunosuppressive, and has gastrointestinal irritative properties that may be attributable to its enterohepatic recirculation (Papageorgiou C,

> *Mini Rev Med Chem.*, 1:71-77 (2001)). Mizoribine aglycone, a prodrug, is used as an IMPDH inhibitor. Other IMPDH inhibitors, including prodrugs of mizoribine and mizoribine aglycone are known and are described in U.S. Patent Application Nos. 60/400,583 and 60/400,568, both filed August 2, 2002 and both of which are herein incorporated by reference.

More disclosure is not required, since "[a] patent need not teach, and preferably omits, what is well known in the art." MPEP 2164.01 *citing In re Buchner*, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 221 USPQ 481, 489 (Fed. Cir. 1984).

The identity of IMPDH inhibitors was known at the time of filing, as were assays to identify such compounds. The Examiner acknowledges as much in the rejections for alleged obviousness, stating ".Albrecht *et al.* discloses a procedure for determining the enzymatic activity of inosine monophosphate dehydrogenase in a patient being treated with an IMPDH inhibitor. . . . These inhibitors are revaelded to be clinically useful for treating deseases including cnacer." Office Action at page 17. As the enablement and obviousness arguments in the Office Action are inconsistent, one or both rejections should be withdrawn.

With regard to the rejection based on the treatment of cancer, claims 64 and 112 are amended to recite "interferon sensitive cancer". In view of the above amendments and arguments, withdrawal of the rejection for alleged lack of enablement is respectfully requested.

V. Rejections under 35 U.S.C. §103(a)

Claims 64-73, 112, and 113 are rejected as obvious under 35 U.S.C. §103(a). The claims are variously rejected as being unpatentable over the disclosure of Hirahashi *et al.* in combination with Tressler *et al.* or Albrecht *et al.* Kirkwood *et al.* and Krug *et al.* are also cited against some claims. Each rejection thus relies upon the Hirahashi *et al.* publication as the primary reference. To the extent the rejection applies to the amended claims, Applicants respectfully traverse the rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met: (1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference must teach or suggest all the claims limitations. MPEP§2143. Recently, in reviewing this standard, the Supreme Court noted that any analysis supporting a rejection under § 103(a) must be made explicit, and that it is "important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the [prior art] elements in the manner claimed." *KSR Intl Co. v. Teleflex Inc.*, 82 USPQ2d 1385, 1396 (U.S. 2007). "This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known." *Id.*

While the Court warned against a "rigid application" of the TSM test, the Court also found that these questions could provide a "helpful insight" in determining whether the claimed subject matter is obvious under § 103(a). *Id.* at 1396-1397. *See also*, Memorandum to Technology Directors from Margaret A. Focarino, Deputy Commissioner for Patent Operations, May 3, 2007. The cited references provide no motivation for their combination and provide no expectation of success to arrive at enhanced interferon production in their combination.

A. Tressler et al. in view of Hirahashi et al.

According to the Office Action Tressler *et al.* discloses a study of the anti-tumor activity of mycophenolic acid and mycophenolate mofetil against various cancer lines. also according to the Office Action, Hirahashi *et al.* discloses that an extract from the cyanobacterium Spirulina is an interferon inducer and thus, is useful to treat cancer. The Office Action reasons that because both mycophenolic acid and mycophenolate mofetil and the Spirulina are allegedly useful to treat cancer, those of skill would expect the combination of therapies to be successful as a cancer treatment. This reasoning is the basis for the *prima facie* case of obviousness put forth by the Office Action. *See, e.g.*, Office Action at page 16.

First, the Office Action provides no specific motivation for the combination of a synthetic interferon inducer and an IMPDH inhibitor, other than reasoning that since both compositions can be used to treat cancer, one of skill would be motivated to combine the compounds for treatment of cancer. As hundreds, if not thousands of compounds, can be used to inhibit growth of cancer cells, based on *e.g.*, in vitro testing, the Office Action provides no motivation for the selection of these two classes of compounds by on e of skill and appears to suggest that those of skill will use any combination of chemotherapeutic compounds for treatment. As amended, the claimed combination also exhibits synergy by increasing the amount of interferon induced and the cited references provide no motivation for those of skill to produce that effect through combination of chemotherapeutic compounds.

Additionally, the Office Action does not provide a reasonable expectation for success in the combination of an IMPDH inhibitor and a synthetic interferon inducer to treat cancer. Although obviousness does not require absolute predictability of success, an invention is *not* invalid for obviousness if the inventor would have been motivated "to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." *PharmaStem Therapeutics Inc. v. ViaCell Inc.*, 83 USPQ2d 1289, 1305 (Fed. Cir. 2007) (quoting *In re O'Farrell,* 7 USPQ2d 1673, 1681 (Fed. Cir. 1988)). Here, the parameters, based on the reasoning in the Office Action, are apparently all chemotherapeutic compounds. The cited references provide no direction as which classes of chemotherapeutic compounds or individual species of chemotherapeutic compounds, would successfully exhibit enhanced interferon induction on their combination. Therefore, a prima facie case of obviousness ha not been established and this rejection for alleged obviousness should be withdrawn.

The remaining rejections for alleged obviousness also cite Hirahashi *et al.* and use similar reasoning.

B. Albrecht et al. in view of Hirahashi et al.

Claims 64-67 are rejected as allegedly obvious over Albrecht *et al.* in view of Hirahashi *et al.* According to the Office Action, Albrecht *et al.* discloses that IMPDH inhibitors can be useful to treat disease including cancer. In fact, Albrecht *et al.* also discloses that the in vivo activity of IMPDH inhibitors is useful to **suppress** the immune system, as is done after organ transplantation. Albrecht *et al* at page 1, lines 31-34. Albrecht *et al.* teach a new method of measuring IMPDH activity in blood samples, with the purpose of using the assay as a correlate for immunosuppression in a patient, particularly a patient who has had an organ transplant. In contrast, the claimed methods are directed to methods of **activating** the immune system by administering both an IMPDH inhibitor and a synthetic interferon inducer, thereby enhancing the activity of the interferon inducer.

Using the same reasoning above, Albrecht *et al.* in combination with Hirahashi *et al.* do not provide a motivation to combine these particular drugs to enhance interferon production. Nor does this combination of references provide an expectation of success in enhancing interferon production by using the claimed methods. Finally, because Albrecht *et al.* disclose use of IMPDH inhibitors as immunosuppressants, this reference actually teaches away from the claimed use of IMPHD inhibitors combined with synthetic interferon inducers to further enhance interferon induction.

C. Albrecht et al. in view of Hirahashi et al. and Kirkwood et al.

Claims 68, 112, and 113 are rejected as allegedly obvious over Albrecht *et al.* in view of Hirahashi *et al.* and Kirkwood *et al.* The disclosures of Albrecht *et al.* and Hirahashi *et al.* are discussed above. According to the Office Action, Kirkwood *et al.* review various studies of the antitumor effects of interferons and it allegedly would have been obvious to modify Albrecht *et al* by administering exogenous type I interferon. Claim 68 depends from claim 64 and thus, the arguments of part B are relevant. Kirkwood *et al.* does not remedy the deficiencies of Albrecht *et al.* and Hirahashi *et al.* argued in part B.

With regard to claims 112 and 113, the references do not provide any rational for the combination of IMPDH inhibitors and interferon, out of all the chemotherapeutic agents that

could possibly be selected by those of skill. Therefore, this combination of references fails to provide a motivation to combine or a reasonable expectation of success in combination as is required for a prima facie case of obviousness.

D. Tressler et al. in view of Hirahashi et al. and Krug et al.

Claims 69-73 are rejected as allegedly obvious over Tressler *et al.* in view of Hirahashi *et al.* and Krug *et al.* The disclosures of Tressler *et al.* and Hirahashi *et al.* are discussed above. According to the Office action, Krug *et al.* discloses a study of the interferon-inducing abilities of CpG oligonucleotides and it allegedly would have been obvious to substitute the IFN-stimulating CpG oligonucleotides of Krug *et al.* in place of the Spirulina extract of Tressler *et al.* Claims 69-73 depends from claim 64 and thus, the arguments of part A are relevant. Krug *et al.* does not remedy the deficiencies of Albrecht *et al.* and Hirahashi *et al.* argued in part B. Even in combination with Tressler *et al.* and Hirahashi *et al.*, Krug *et al.* does not provide a motivation to combine an IMPDH inhibitor with an interferon inducer to enhance interferon production. Nor does this combination of references provide an expectation of success in enhancing interferon production by using the claimed methods.

In view of the above amendments and remarks, withdrawal of the rejection for alleged obviousness is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments

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